

Applicant: Jay M. Short
U.S. Serial No.: 09/375,605
Filing Date: August 17, 1999

Docket No.: DIV-1140-2

Remarks:

First, applicant wishes to thank the Examiner for the interviews in connection with the subject application. Applicant believes those meetings were extremely helpful in moving forward the prosecution of this application.

Claims 41-50 and 56-72 were pending. Applicant canceled claims 41-50 and 56-72 herein without prejudice and have introduced new claims 73-93 to be the basis of further examination. Claims 73-93 are fully supported by the application and claims as filed, and no new matter has been introduced into the application. Support for claims 73-93 may be found, *inter alia*, in the specification on page 3, last paragraph, to page 4, lines 1-6; on page 5, last paragraph and page 10, first paragraph; on page 9, lines 10-14; on page 9, lines 3-9; on page 30, last four lines of the first paragraph; and on page 4, paragraphs 2-4 to page 5, paragraphs 1 and 2. Thus, claims 73-93 will be pending and under exam upon entry of this amendment.

Objection to Claim 72

The Examiner has objected to claim 72 (drawn to enzymatic activities) as containing multiply patentably distinct species (*i.e.*, hydrolase, polyketide synthase, alkaline phosphatase, and β -glycosidase). In addition, claim 72 has been objected to under 37 CFR §1.75(d)(1) for stating an improper Markush group.

In response, but without conceding the correctness of the Examiner's position, applicant has canceled claim 72 and added claims to recite the members of the previous Markush group separately. Applicant requests that the Examiner reconsider and withdraw this rejection.

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Objection to Specification

The specification has been objected to as failing to provide proper antecedent basis for the subject matter of claims 44-50. In reply, claims 44-50 are cancelled without prejudice and it is believed that the claims as currently presented overcome this objection. Accordingly, withdrawal of the objection is respectfully requested.

Rejections Under Doctrine of Obviousness-Type Double Patenting

Claims 41-50 and 56-72 stand rejected under the doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-12 of U.S. Patent No. 5,939,250. Claims 41-50 and 56-72 stand rejected under the doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 5,958,672 in view of the prior art as exemplified by Arnold et al. (U.S. Patent No. 5,316,935).

In reply, but without conceding the correctness of the Examiner's position, applicant stands ready to submit Terminal Disclaimers under 37 C.F.R. §1.321(c), executed by the assignee, along with the fee as required under 37 C.F.R. §1.20(d) to obviate these rejections. However, since there are other issues remaining in this case, applicant requests that the Examiner hold these rejections under the doctrine of obviousness-type double patenting in abeyance until the claims are deemed to be in condition for allowance.

Rejections Under 35 U.S.C. §112, second paragraph

Claims 41-50 and 56-72 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claim 41 is said to be drawn to an incomplete method because it is considered by the Examiner to be missing essential steps.

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In reply, without conceding the correctness of the Examiner's position, applicant has canceled claims 41-50 and 56-72 and has presented new claims 73-93 for further consideration. It is believed that the claims as presented herein clearly describe the subject matter which the applicant regards as the invention and address the Examiner's concerns. Applicant requests that the Examiner reconsider and withdraw this ground of rejection.

Rejections Under 35 U.S.C. §102

Claims 41-50 and 56-72 stand rejected under 35 U.S.C. §102(e) as being anticipated by Thompson et al. (U.S. Patent No. 5,824,485; "the '485 patent"). The Examiner remarks that applicant's arguments filed on 9/9/02 are not deemed persuasive.

Claims 41-50 and 56-72 have been cancelled, thus obviating this rejection. In order to speed prosecution of newly added claims 73-93, however, Applicant will discuss the cited reference. Applicant respectfully traverses this rejection. It is respectfully submitted that the claims as presented herein are not anticipated by the '485 patent to Thompson et al. under 35 U.S.C. §102(e).

The presently claimed invention is directed to a method for identifying a protein having a desired activity, the method comprising: (a) constructing a DNA library from DNA molecules obtained directly from an unselected environmental source; (b) mutagenizing at least one member of the library, wherein one or more DNA molecules of the library are mutated; (c) expressing the library to produce one or more proteins; and (d) screening the proteins produced in (c) to identify one or more protein(s) with the desired activity.

Thompson et al. fail to teach every element of the claimed invention prior to the time of applicant's presently claimed invention. Because the '485 patent to Thompson et al. fails to

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disclose each and every element of applicant's claimed invention as of the time of each of its priority application filing dates, this reference fails to anticipate the presently claimed invention.

To anticipate under 35 U.S.C. §102(e), a patent reference must have been filed in the U.S. before the applicant's invention. Accordingly, the effective filing date of the Thompson et al. '485 patent must be earlier than that of the instant application. In addition, under §102, a reference must disclose each and every limitation of a claimed invention. *Apple Computer, Inc. v. Articulate Systems, Inc.*, 234 F.3d 14, 57 USPQ2d 1057 (Fed. Cir. 2000; *Brown v. 3M*, 265 F.3d 1349, 60 USPQ2d 1375 (Fed. Cir. 2001). It is submitted that neither of Thompson et al.'s priority documents discloses or teaches what is presently claimed by the applicant. Thus, Thompson does not anticipate applicant's present claims.

For the Examiner's convenience in assessing the disclosure and teachings of the priority documents of Thompson et al., as well as the disclosure of the '485 patent, the applicant provides herewith marked-up copies of the two priority patent applications of Thompson et al., namely, U.S. Serial No. 08/427,348, filed April 24, 1995 ("the '348 application") and U.S. Serial No. 08/427,244, filed April 24, 1995 ("the '244 application") (**Exhibit A**). The teaching and disclosures of these applications and the '485 patent are discussed further below.

As indicated by the highlighted portions of the priority applications, both priority documents reveal a clear lack of disclosure and teaching of methods involving nucleic acids obtained directly from an unselected environmental source. Specifically, the relevant disclosure of selected microorganisms, or selected species of microorganisms, for use in the methods described in the '348 application is found on page 4, lines 5-9; page 7, lines 3-7; page 8, lines 30-35; and page 9, lines 8-12. In addition, the relevant disclosure of selected bacterial species for use in the methods described in the '244 application is found on page 15, lines 13-15; on

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page 16, "Preparation of Donor Genomic DNA", lines 19-20; and on page 6, lines 22-24, where marine is isolated from an estuarine *bacterium*.

It is also apparent that the disclosure in the '485 patent relating to "genetic material being obtained from any organism including those from environmental samples" (Cols. 12-16) and the "isolation of nucleic acid sequence from soil or other mixed environmental samples (uncultured)", (Section 5.3.6, Col. 41 of Thompson et al.) was newly added to the CIP application leading to the '485 patent, *i.e.*, U.S. Serial No. 639,255, at the time of filing the '255 application on April 24, 1996. Indeed, the two priority applications of Thompson et al. are silent with respect to directly obtaining nucleic acid from donor microorganisms from an environmental sample without an initial isolation or selection process.

In addition, Thompson et al. do not teach or suggest subjecting the library to mutation prior to screening. To the extent that Thompson et al. discuss mutation at all, it is limited to circumstances following screening and selection of the library clones (see Col. 10, lines 11-16)

In view of the foregoing, it is respectfully requested that the rejection under §102(e) over Thompson et al. be withdrawn.

Rejection Under 35 U.S.C. §103

Claims 41-50 and 56-72 were rejected under 35 U.S.C. §103 as being unpatentable over Thompson et al. (U.S. Patent No. 5,824,485, "the '485 patent") in view of the state of the art as exemplified by the cited art, Stemmer (1994, *Proc. Natl. Acad. Sci. USA*, 91:10747-10751) and Arnold et al. (U.S. Patent No. 5,316,935) for reasons set forth in prior Office Action.

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Claims 41-50 and 56-72 were rejected under 35 U.S.C. §103 as being unpatentable over Radomski et al. (U.S. Patent No. 5,849,491, “the ‘491 patent”) in view of the state of the art as exemplified by the cited art, Stemmer (1994, *Proc. Natl. Acad. Sci. USA*, 91:10747-10751) and Arnold et al. (U.S. Patent No. 5,316,935).

Claims 41-50 and 56-72 have been cancelled, thus obviating these rejections. In order to speed prosecution of newly added claims 73-93, however, Applicant will discuss the cited combinations.

As an initial matter, Applicant respectfully submits that to date the Patent Office has failed to state a *prima facie* case for obviousness. The burden of proof in establishing a *prima facie* case of obviousness under § 103 clearly rests with the Patent Office. *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984). In establishing a *prima facie* case, the Patent Office, among other things, must show that (1) the prior art would have suggested to those of ordinary skill in the art that they should make the claimed invention and (2) that the prior art would have revealed a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). “Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the applicant’s disclosure.” *Id.* Thus, “particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.” *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000). Further, when relying on the knowledge of persons of ordinary skill in the art, the Patent Office must “explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination.” *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). “The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record.

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This precedent has be reinforced in myriad decisions, and cannot be dispensed with.” *In re Sang Su Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002) (citations omitted).

To date, the Patent Office has failed to provide objective evidence of any suggestion or motivation in the prior art to combine and modify the particular references cited by the Office. Instead, the Office has simply recited elements gleaned from the various references and stated that the combination of these elements would have been obvious to one skilled in the art. It is well settled that the Patent and Trademark Office cannot pick and choose among the individual elements of assorted prior art references to recreate the claimed invention. SmithKline Diagnostics, Inc. v. Helena Laboratories Corp., 859 F.2d 878, 887 (Fed. Cir. 1988). In addition, it is now well established that “[b]road conclusory statements regarding the teaching of multiple references standing alone are not ‘evidence’.” *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999); see also *In re Kotzab*, 217 F.3d at 1370. “Th[e] factual question of motivation is material to patentability, and [can] not be resolved on subjective belief and unknown authority.” *In re Sang Su Lee* 277 F.3d at 1343-44. Without such objective evidence to combine the references, it is inferred that the references were selected with the assistance of hindsight. *In re Rouffet*, 149 F.3d at 1358. It is well-established that the use of hindsight in the selection of references that comprise a case of obviousness is forbidden. *Id.*

Thompson et al.

Applicant respectfully traverses the rejection based on Thompson et al. in light of Stemmer and Arnold et al. Because Thompson et al. fails to anticipate under §102(e), it, in turn, cannot make obvious the presently claimed invention, since any relevant teaching in Thompson

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does not appear until the April 24, 1996 filing date of the application leading to the '485 patent, a date which is after applicant's effective filing date.

None of the cited references, alone or in combination make obvious applicant's presently claimed invention. Neither Arnold et al., nor Stemmer ., teache or describe processes involving nucleic acids that are directly obtained from an unselected environmental source. Indeed, Arnold et al. utilize particularly isolated subtilisin DNA fragments. Such starting material is antithetical to applicant's method comprising DNA molecules obtained directly from an unselected environmental source. Likewise, Stemmer discloses *in vitro* recombination of homologous genes. The use of homologous genes requires a high degree of selection in contrast to the present invention in which unselected DNA molecules are used.

Based on the disclosures and teachings of the cited references, Applicant submits that one of ordinary skill in the art would have no motivation to combine the references and that the Patent Office has failed to identify any objective teaching in the prior art of such motivation. In addition, even if combined, the references do not teach the presently claimed invention and thus put the public in possession of the invention as a whole as required to support a finding of obviousness. See *Rockwell Intl. Corp. v United States*, 147 F.3d 1358 (Fed. Cir. 1998). It is respectfully requested that this rejection under §103 be withdrawn.

Radomski et al.

Applicant respectfully traverses the rejection based on Radomski et al. in light of Stemmer and Arnold et al. Radomski et al. discloses the amplification of genetic material encoding modified or different xylanase enzymes obtained from xylanases located in soil sample components. Unlike the present invention, Radomski et al. fails to teach or disclose

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mutagenizing nucleic acids directly obtained from an unselected environmental source, to produce a protein having a desired activity.

Stemmer discloses reassembly of genes from random DNA fragments from homologous genes resulting in *in vitro* recombination. In accordance with the methods of Stemmer, different combinations of DNA fragments recombine by random crossovers so as to result in a reassembled gene having various mutations that can be determined by sequencing. Stemmer does not teach or suggest the use of unselected DNA molecules.

Arnold et al. describe the mutation of subtilisin genes to create subtilisins having improved properties, *e.g.*, catalysis. Arnold et al. neither teach nor describe processes involving nucleic acids that are directly obtained from an unselected environmental source. Indeed, Arnold et al. utilize particularly isolated subtilisin DNA fragments. Such starting material is in contrast to applicant's method comprising DNA molecules obtained directly from an unselected environmental source.

The primary reference of Radomski neither teaches nor suggests applicant's invention as claimed. Based on their respective teachings, neither Stemmer nor Arnold compensate for the deficiencies of Radomski et al. To date, the Patent Office has not identified objective evidence in the prior art of motivation for one of skill in the art to combine Radomski (related to the isolation of different xylanases from soil samples, and using these isolates for new enzyme activities, and their sequences as the source of variant sequence information to produce mutant, constructed xylanases out of known and standard xylanase sequences) with Stemmer (related to a type of DNA mutagenesis described by Stemmer involving the mixing of DNA fragments to assemble "new genes by recombination *in vitro*"), or with Arnold et al. (which is specific for the mutagenesis of subtilisin from particularly isolated and/or cloned DNA sources). In addition,

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Applicant respectfully submits that even if combined, the references do not teach the presently claimed invention and thus put the public in possession of the invention as a whole as required to support a finding of obviousness. See *Rockwell Intl. Corp. v United States*, 147 F.3d 1358 (Fed. Cir. 1998).

In view of the foregoing, it is respectfully requested that the Examiner reconsider and withdraw the rejections under §103.

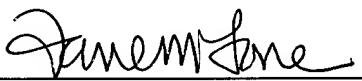
Conclusion:

Applicant hereby gives authorization for payment of any additional fee deemed necessary, other than an issue fee, to be charged to Deposit Account No. 08-0219.

If there are any questions concerning this application, the Examiner is invited to call the undersigned attorney at her telephone number indicated below.

Respectfully submitted,

Date: May 19, 2003

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